REMARKS

Claims 122, 185, 189, 192, 197, 200, 221-224, 226, 228-232 are pending and under active consideration.

In the present Amendment, the status identifier of the withdrawn claims has been corrected to recite "withdrawn." The amendment to claim 205 originally made in the Amendment of February 14, 2007 has been reintroduced, in view of the Examiner's comment that the status of claim 205 had been identified as "Previously presented" instead of "Currently amended."

It is believed that no new matter has been added by the amendment made herein. Entry of the foregoing amendment is respectfully requested.

INTERVIEW SUMMARY RECORD

Applicants and Applicants' representatives thank Examiner Mark Staples for the courtesy of the telephonic interview dated August 14, 2007 in connection with the above-identified application (the "Interview") between Examiner Mark Staples, Applicants' representatives Adriane M. Antler and Muna Abu-Shaar, Assignee's representative Eileen Sun, and Inventor Chris Armour in connection with the above-referenced application. Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. 713.04, Applicants present this Interview Summary Record of the Interview

During the Interview, the Office Action dated May 15, 2007 (the "May Office Action") was discussed. Regarding the obviousness rejection under 35 U.S.C. § 103, Dr. Antler explained why, as substantially set forth below, the prior art relied upon by the Examiner in the instant Office Action, U.S. Patent No. 6,329,140 by Lockhart ("Lockhart"), Bowtell, 1999, Nature Genetics Supplement 21:25-32 ("Bowtell"), and Schena *et al.*, 1996, Proc. Natl. Acad. Sci. U.S.A. 93:10614-19 ("Schena"), did not make obvious the subject matter of the instant claims. The Examiner expressed appreciation for the explanation and indicated that he would reconsider the the cited literature in view of Applicants' explanation and perform a new search.

Dr. Antler also noted to the Examiner that in the Disposition of Claims in the Office Action Summary for the May Office Action, the Examiner erroneously indicated that claims 122, 185, 189, 192, 200, 217, 220-224, 226 and 228-232 are pending, with claim 220 being withdrawn from active consideration. However, the pending claims are claims 122, 178, and

185-232, with claims 178, 186-188, 190-191, 193-196, 198-199, 201-220, 225 and 227 being withdrawn from consideration. Appropriate correction was requested.

Next, Dr. Antler requested clarification from Examiner Staples regarding the status of claims 185 and 232 which, though indicated to be rejected on the Office Action Summary page of the May Office Action, had not been subject to a prior art-based rejection at any stage of the prosecution of the present application. In response, Examiner Staples indicated that he would consider this issue further following the Interview. In subsequent phone calls to Dr. Antler, Examiner Staples explained that he would issue a new Office Action which would supercede the May Office Action and in which claims 185 and 232 would be finally rejected.[1]

Details of the arguments in response to the rejections under 35 U.S.C. § 103 presented in support of patentability are found hereinbelow.

THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

The rejection of claims 122, 185,[2] 189, 192, 197, 200, 221-222, 224, 226 and 228-232 under 35 U.S.C. § 103 as obvious over U.S. Patent No. 6,329,140 by Lockhart ("Lockhart") and Bowtell, 1999, Nature Genetics Supplement 21:25-32 ("Bowtell") is maintained for the reasons of record. Also maintained is the rejection of of claim 223 as obvious of Lockhart in view of Bowtell, and further in view of Schena *et al.,* 1996, Proc. Natl. Acad. Sci. U.S.A. 93:10614-19 ("Schena"), for reasons also of record. Applicants respectfully disagree, for the reasons discussed below.

The presently claimed invention relates to positionally-addressable ordered arrays of polynucleotide probes bound to a solid support; wherein the polynucleotide probes comprise at least 100 polynucleotide probes of different nucleotide sequences, each said different nucleotide sequence comprising a sequence complementary and hybridizable to a different genomic sequence of the same species of organism, wherein the respective genomic sequences complementary and hybridizable to the probes are found at sequential sites in the genome.

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[1] The new Office Action issued August 17, 2007, and is the subject of this response. In the new Office Action, the disposition of the claims has been corrected, and claims 185 and 232 have been rejected on the same 35 U.S.C. § 103 grounds as the other claims.

[2] Although claim 185 is not listed in the statement of the rejection under 35 U.S.C. § 103 in paragraph 12 on page 5 of the Office Action, it is listed in paragraph 14 beginning on page 8 of the Office Action and is discussed on page 9 of the Office Action.

The arrays are characterized by a *high density* of the genomic sequences complementary to probes in the genome (because the the distance between 5′ ends of the sequential sites is always less than 500 bp); and a *large span* (or, as referred to by the Examiner, a "*long span*") of the genomic sequences (because the genomic sequences complementary and hybridizable to the of probes span a genomic region of at least 25,000 bp).

According to the Examiner, Bowtell teaches the *long span* feature of the claims, while Lockhart teaches the *high density* feature of the claims (Office Action at page 5). The Examiner further contends that "Bowtell provides the motivation to combine the long genome span with high density of Lockhart et al." The Examiner contends that such motivation is provided by the following:

- Bowtell states many benefits of spanning a genome, such as by stating that "[o]btaining the entire genomic sequence of *S. cerevisiae* allowed a near-complete set of genes to be generated by PCR, which have been arrayed and analyzed" (citing to Bowtell at page 29, second sentence of the first full paragraph of the right column[3]);
- Bowtell describes the goal of the use of DNA microarrays, which goal was for comprehensive RNA expression analysis;
- Technical developments could permit scrutinizing all genes for a given organism, and microarray-based expression analysis offers a powerful tool for this purpose.

Office Action at page 6, first full paragraph.

Firstly, Applicants emphasize that Bowtell deals solely with expression analysis, *i.e.*, the author is interested in analyzing expression of genes. Bowtell is not concerned with geome sequences that are not expressed (such as introns, intergenic regions, and promoter sequences). Even if the Examiner were correct that Bowtell indicates a goal or desire to monitor expression of every gene in a genome, the Examiner wrongly presupposes that an array for such comprehensive analysis of gene expression will have probes at the high density called for by the claims, in which the 5′ ends of the sequential sites to which the probes are

[3] The Examiner incorrectly cites to page 29, second sentence of the first paragraph of Bowtell for this quote.

complementary is always less than 500 bp. Applicants respectfully submit that this conclusion --*i.e.*, that a comprehensive gene expression array would have, or would be expected to have, the *high density* feature of the claims-- is in error, and further submit that the rejection under 35 U.S.C. § 103 should be withdrawn.

The error in the Examiner's reasoning is exemplified by the publication to which Bowtell refers on page 29 (in the text cited by the Examiner) regarding the arraying and analysis of a near-complete set of *S. cerevisiae*, *i.e.*, yeast, genes. This publication, DeRisi *et al.*, 1997, Science 278:680-686 (attached hereto as Exhibit 1), describes the generation of microarrays containing probes to 6000+ *S. cerevisiae* genes for analyzing gene expression (RNA transcript) patterns (see DeRisi at page 685, right column and note 8). Each probe resulted from PCR amplification of a known or predicted open reading frame in the *S. cerevisiae* genome (see DeRisi at page 685, note 8). Applicants respectfully direct the Examiner's attention to Exhibit 2, Goffeau *et al.*, 1996, Science 274:546, 563-567 ("Goffeau") at page 546, right column. Goffeau discloses that in the *S. cerevisiae* genome, a protein-encoding gene (containing an open reading frame) is found for every 2 kb of the *S. cerevisiae* genome. Thus, each pair of probes corresponding to open reading frames of adjacent genes in the *S. cerevisiae* genome as taught by DeRisi would be complementary to sequential sites in the *S. cerevisiae* genome whose 5′ ends are, on average, 2 kb apart (schematized in Exhibit 3A).[4] In contrast, the microarrays of the claims contain *high density* probes that are complementary to sequential sites in a genome whose 5′ ends are *always less than 500 bp* apart (see Exhibit 3B).[5] There is no disclosure, hint or suggestion in Bowtell (or

[4] Moreover, 70% of the total sequence of the *S. cerevisiae* genome consists of open reading frames (Goffeau at page 546, right column, last paragraph). Thus, 30% of the *S. cerevisiae* genome, or 0.6 kb of each 2 kb interval at which an open reading frame is found, represents non-coding sequence. This means that the open reading frames to which DeRisi's probes are complementary are separated by on average 0.6 kb. Accordingly, even if the probes in a full genome *S. cerevisiae* expression array were complementary to just a portion of each open reading frame (which Applicants note is not taught by DeRisi), because each open reading frame is separated from neighboring open reading frames by, on average, 0.6 kb (since only 4% of the *S. cerevisiae* genome contains introns, and these 4% usually only have one small intron close to the start of the coding sequence; see Goffeau at page 563, middle column, first paragraph), the 5′ ends of the genomic sequences to which the probes are complementary would still be on average greater than 0.6 kb.

[5] Exhibit 3B is a depiction of one exemplary embodiment of the claims in which the probes are complementary to adjacent sequences that abut one another in the genome. This depiction should not be viewed as limiting the claimed arrays in any way, since other probe configurations, such as, for example, overlapping or spaced probes are also within the scope of the claimed invention.

DeRisi) to tile across noncoding sequences such that the 5' ends of the complementary genomic sequences would be less than 500 bp apart. In fact, such would run counter to common sense, since Bowtell and DeRisi are concerned with expression analysis.

Moreover, as explained by Goffeau, "[t]he yeast genome is much more compact than those of its more complex relatives in the eukaryotic world. By contrast, the genome of the nematode worm contains a potential protein-encoding gene every 6 kb, and in the human genome, some 30 kb or more of sequence must be examined in order to uncover such a gene" (Goffeau, paragraph spanning page 563, left column). Thus, based on knowledge in the art as of the effective filing date of the instant application, an array for monitoring the entire nematode or entire human genome, containing a probe for each gene as taught by DeRisi, would be expected to contain probes that are complementary to sequential sites in the genome whose 5' ends are separated on average every 6 kb or every 30 kb, respectively.

In other words, an array that is capable of monitoring gene expression of the entire relatively compact *S. cerevisiae* genome, though possessing the *large span* called for by the claims, does not possess the *high density* of the claims (wherein probes are complementary to sequential sites in the genome whose 5' ends are separated by less than 500 bp). Moreover, there is no common sense reason for one of skill in the art to generate a *high density* array as called for by the present claims. *See KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742-43 (2007). Lockhart does not provide that common sense reason, since Lockhart uses tiling arrays to determine whether a given gene possesses a sequence signature of up to 300 nucleotides or up to 300 amino acids (Lockhart at Abstract, column 1, lines 50-59 and column 7, line 35 to column 8, line 12). Lockhart does not provide any common sense reason to tile across noncoding sequences that do not have a sequence signature of interest. Thus, there is no discernible reason, and thus no motivation, in the combination of Lockhart and Bowtell to create an array with a probe set having the *long span* and *high density* features of the claims.

Indeed, the arrays of the claims are "more than the predictable use of prior art elements according to their established functions." *See KSR*, 127 S.Ct. at 1740 (citing *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969) and *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273 (1976)). For example, the presently claimed arrays by virtue of their long span and high density give rise to a function that is not afforded by the elements of Bowtell and Lockhart relied on by the Examiner, that is the long span of Bowtell or the high

density of Lockhart. In particular, the claimed arrays can be employed to precisely identify the boundaries of expressed genes in genomic sequences, for example by delineating intron/exon boundaries, without extensive DNA sequencing of ESTs (see specification at page 3, lines 13-28 and page 4, lines 1-21). This is more than the predictable use of the elements of Lockhard and Bowtell according to their established functions: Lockhard uses tiling arrays for signature sequence identification, thereby identifying gene family members having a particular sequence signature. In fact, Lockhart teaches to avoid tiling over regions that are near expected intron/exon boundaries, thus clearly teaching away from the utility afforded by the claimed invention:

> The interrogated regions were chosen based on a few criteria: they include regions that are (a) reasonably well conserved (highly conserved at the amino acid level, but less so at the DNA level) and that serve as identifiers of the protein family, (b) highly variable and serve as unique identifiers of individual members of the family, and (c) not near expected intron/exon boundaries.

(see Lockhart at col. 27, lines 11-17). Bowtell uses arrays to determine whether genes are expressed rather than determining the boundaries of expressed sequences. Thus, any elements of Lockhart and Bowtell appearing in the claimed invention are not used according to their predictable functions.

Therefore, claims 122, 185, 189, 192, 197, 200, 221-222, 224, 226 and 228-232 are not made obvious by Lockhart and Bowtell, and the rejection of these claims should be withdrawn.

Finally, with respect to claim 223, the Examiner is using Schena for its disclosure that a high throughput approach of "microarrays of cDNA clones as gene-specific hybridization targets [had been successful] to quantitatively measure expression of the corresponding plant genes" (Schena at page 10614, left column second paragraph after Abstract), to support the alleged obviousness of the added limitation of claim 223.

Applicants point out that Schena suffers from the same deficiencies as Bowtell, since Schena is concerned with the use of microarrays containing 1046 random human cDNA clones from a library of Epstein-Barr virus-transformed human peripheral blood lymphocytes, with 10 *Arabidopsis* clones as controls, for monitoring gene expression (Schena at page 10614, under "Materials and Methods"). Thus, like Bowtell, Schena is directed at the

analysis of gene expression, in this case using cDNAs as probes, with the goal of monitoring expression of the entire human genome. For the same reasons explained above, one of skill in the art at the effective filing date of the present application would have expected human genes to be separated by 30 kb on average and, accordingly, cDNAs corresponding to adjacent genes to have 5′ sequences complementary to sequences that are, on average, at least 30 kb apart. In contrast, the claims of the present invention call for a distance between 5′ ends of sequential sites of less than 500 bp. Schena provides no motivation to tile across noncoding regions, since it is concerned only with expression analysis. Accordingly, there is no common sense reason, and thus no motivation, in Schena to create an array with a probe set having the *high density* features of the claims. *Cf. KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742-43 (2007). Schena's mention by way of background that arrays had been used to measure the expression of plant genes, which is the Examiner's reason for citing Schena, does not provide such a reason.

Accordingly, Schena does not remedy the deficiencies of Lockhart and Bowtell.

Conclusion Regarding Obviousness

In view of the foregoing remarks, it is submitted that the obviousness rejections are in error and should be withdrawn.

CLAIMS WITHDRAWN FROM CONSIDERATION AS BELONGING TO NON-ELECTED SPECIES SHOULD BE CONSIDERED

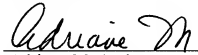
Claims 186-188, 190-191, 193-196, 198-199, 201-220, 225 and 227 were withdrawn from consideration by the Examiner as belonging to non-elected species. Since Applicants believe that the generic claims are allowable, claims 186-188, 190-191, 193-196, 198-199, 201-220, 225 and 227 should be considered by the Examiner. Applicants respectfully request that these claims be considered by the Examiner.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants respectfully request that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney if a telephone call would help resolve any remaining items.

Respectfully submitted,

Date: October 31, 2007



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Enclosures

Exhibit 3A

DeRisi microarray probes

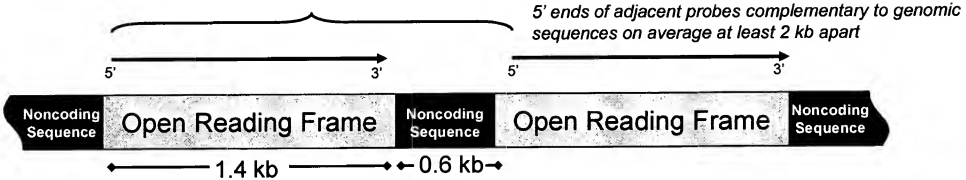

Exhibit 3B

Claimed microarray probes